Conclusions.

Tuberculin is specific in diagnosis, for:

- (1) It is a reagent derived from bacilli of the same species as the infection;
- (2) the non-infected, whether healthy or suffering from any other disease, do not react;
- (3) the infected react unless protected by artificial tolerance or too exhausted to respond;
- (4) the local reaction shows that the patient has been infected; the general reaction shows that the tubercle bacilli are alive; the focal reaction shows the seat of the disease;
- (5) experience in animals confirms that in men.

Tuberculin is specific in treatment, for:

- (6) tolerance to tuberculin and immunity to tuberculosis increase together;
- (7) tuberculin acts by stimulating the *vis medicatrix naturae*;
- (8) increasing doses of tuberculin overcome the initial sensitiveness;
- (9) large doses are required for prolonged good;
- (10) if on cessation of tuberculin the immunity lapse it may be rapidly restored on resumption;
- (11) tuberculin is ineffective against streptococci and other non-tuberculous infections: it is specific.

The evidence outlined in this article is given at length in such publications as:

Tuberculin in the Diagnosis and Treatment of Tuberculosis. W. Camac Wilkinson, James Nisbett, London, 1912.
Tuberculin in Diagnosis and Treatment. Bandelier and Roepke. John Bale, Son and Danielsson, London, 1913.
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PEPTONED SERUM AGAR IN ASTHMA.

BY

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It is now over ten years since I tried the injection of peptone in asthma. The peptone used then was the same as I use now—namely, Armour's No. 2. I have tried many others, but some are dangerous, as they contain histamine (Witte's, etc.), and others feeble, as they contain little proteose. It is very important to observe these facts.

In the autumn of 1916 I commenced using the peptone in the case of a non-commissioned officer in the Military Hospital at Mile End.¹ I gave it subcutaneously, but, as I subsequently found, in much too large a dose; this was rectified, and I introduced the intravenous method, published in the following year.² The patient, aged 35, was subject about every three weeks to asthmatical attacks which lasted several days. After the peptone injections he had no attack, and he remained well. This gave me encouragement to continue and try it in others.

The treatment was not given haphazard, but was based on the experimental work of Dale, Biedl and Kraus, Auer and Lewis, Meltzer, etc. The peptone seemed to me to imitate the anaphylactic poison very closely in animals, and it might desensitize against it.

A large number of substances, crystalline as well as colloidal in nature, can produce, on first injection into the guinea-pig, a group of symptoms which are practically indistinguishable from that due to true antigen-antibody anaphylaxis. Fall in blood pressure, leucopenia, diminished coagulability of the blood, and immobilization of the lungs are all present. So is eosinophilia. The difference between these and true anaphylaxis lies in the fact that these substances produce the symptoms on first injection into the normal non-sensitized animal. Karsner and Hanzlik hence called these phenomena "anaphylactoid reactions." Of these substances peptone is most important clinically, as it is the best desensitizer and it produces no symptoms of anaphylaxis. Several authors have stated that it is the

most powerful desensitizer they know of. In 1921 Dale found that peptone desensitized the sensitized guinea-pig.³

When injected into the blood, peptone in 5 per cent. solution produces no symptoms up to the maximum dose ($2\frac{1}{2}$ to $3\frac{1}{2}$ c.cm.) in the large majority of cases. In some persons, however, it does produce a reaction, but these are sensitive to it. In a former paper when I mentioned that a slight reaction might be induced, this was after adding a little Witte's peptone, but as a rule I do not think it is of material benefit, except in a few cases. Peptone produces no precipitins. Some years ago I took the serums of patients well treated with Armour and Witte's peptones to the Lister Institute for examination, and no precipitins could be found by Dr. Arkwright. The same is probably true for other substances producing the anaphylactoid effects. Peptone is probably directed against the antigen-antibody product.

The effect of peptone on human beings differs very greatly, but this is true also in regard to animals. In some persons asthma or migraine very readily yields to it, while others are but little affected; an intermediate state is found in others. This is very difficult to account for. I shall give one or two illustrative cases.

A woman, aged 27, Londoner, sent to me by Dr. Embleton of University College, began to have asthma at the age of 7. She was very bad from 10 to 17, and from 17 to 21 lost it. Then it began again; she had it every few weeks. She stayed in bed a week with it. Vaccines were of no use. She tried Abrams's treatment in 1923; had no asthma while there. Her great-aunt had it. There was no emphysema. Her chest expanded 3 inches. Menses and bowels quite regular. No endocrine defect. No reaction to any protein. I had her for more than two months under treatment with peptone intravenously. I gave Lugol's iodine often in the peptone, and also parathyroid gland in small doses. She had peptone continuously up to $3\frac{1}{2}$ c.cm. Her diet also was considered. No benefit was produced at any time. I then asked her to try serum peptone, but she refused.

There was nothing about this patient to distinguish her from those who do react. If the peptone is directed against the antigen-antibody product, why does it not act here? In regard to iodine and parathyroid, I have repeatedly tried them, but do not consider they add any value to the peptone. In fact, parathyroid was tried because most asthmatics are believed to have a deficiency of calcium in their blood. Now for the opposite effect:

A man, aged 55, is asthmatic and subject also to hay fever. He also frequently has bronchitis and sneezing. Sometimes the asthma is so bad that he gets no rest by day or night. Brings up much sputum. Vaccines from his own sputum did no good. He had twelve peptone injections and was quite well at the end of July last year. Then he returned on September 16th as he had a little asthma in August. I gave him peptone intravenously up to $3\frac{1}{2}$ c.cm., then down to 2 c.cm., $1\frac{1}{2}$ c.cm., and 1 c.cm. He also had five treatments with antiscarrin vaccine for his bronchial trouble. He has remained perfectly free of asthma ever since. I may mention that he gave a marked hay fever cutaneous reaction with 500 units of pollen.

Such a case seems to demonstrate that we should always begin with peptone. Let it be tried for from twelve to sixteen injections. The cases which get better form a much larger percentage than those which do not.

A great many asthmatics give no dermal reaction to proteins. Most people over 45 give none, but I have found one or two severe ones to wheat, etc., in elderly persons. Young people give most reactions, but unless the reaction is to feathers, etc., the peptone will usually clear it. They often outgrow the tendency to asthma.

PEPTONED SERUM AGAR.

It has been stated above that some cases of asthma resist peptone. For such I thought out two or three years ago a modification of the peptone treatment by diluting it with the patient's own serum. In 1922 the findings of Karsner and Ecker were that non-specific desensitization with homologous serum in guinea-pigs is more effective than desensitization with heterologous serums. In the former also there were no deaths, while in the latter there were many from anaphylaxis. It is very dangerous to give a foreign serum to an asthmatic, as one drop of horse serum has been fatal. Again, Dale and Kellaway's experiments on non-specific desensitization showed that homologous serum was well fitted for this in guinea-pigs. I treated the serum of human beings with peptone by adding the peptone immediately to the drawn blood, and incubating

until next day at 37° to 40° C. The serum peptone was then pipetted off. The results were eminently satisfactory. Owing to some change in the peptone it latterly gave a coagulum of serum, plasma, and peptone.⁴ The last case for which I made the serum peptone did extremely well. It was for a patient of Dr. Conder of Cheltenham.

A woman, aged 40, seen in February, 1926, first had asthma at 15. She had migraine very bad previously. Her father had migraine also, and a brother and a cousin had asthma. The asthma was better when she was carrying her two children. There was no response to protein tests. Teeth good; chest expands 2 inches. She had been treated with peptone frequently by Dr. Conder, who has a wide experience of it, but though she improved she was never quite well. I made serum peptone and sent it to Dr. Conder, giving him the dosage. It was given intravenously. In June, 1926, Dr. Conder wrote that she was wonderful, and in February of this year he reported her still quite well.

As the serum peptone was coagulated, I had to consider a new method. Now Dale and Kellaway⁵ found that agar was the most powerful of the agents they used for producing anaphylactoid symptoms. Novy found the same, and states that it is thirty-three times as powerful as peptone for the production of anaphylatoxin. Dale and Kellaway found that agar sol produced death in the sensitized guinea-pig which was quite indistinguishable from that of anaphylactic shock. Agar anaphylatoxin also, in the isolated uterus, gave a pronounced contraction, while the anaphylatoxins of starch and bacteria gave none. In regard to non-specific desensitization, they made a very important observation. When guinea-pigs sensitized to egg albumen were given two doses of agar anaphylatoxin and thus rendered tolerant to it, and then, in twenty-five minutes, were given a dose of egg albumen, they died in five minutes. But when fifty-five minutes were allowed between the anaphylatoxin doses, and two and a quarter hours after the second of these the egg albumen was given, there was absolute protection. Dale thought this was due to "a disturbance in the relation of antibody in the tissues and circulating fluid"; that, in fact, the antibodies had left the cells and gone into the blood, thus causing protection. Shortly after these experiments Kellaway and Cowell,⁶ using homologous serum for guinea-pigs, found that the antibody entirely leaves both cells and blood. It returns very shortly to the cells, but not to the blood until the following day. This disproved Dale's theory. They also found that an entirely different result followed the injection of peptone into guinea-pigs. Using Armour's No. 2, the antibodies remained entirely in the cells, but two-thirds of them disappeared from the blood.⁷ Here was a condition which was excellent for the antigen to cause anaphylaxis (according to Dale), yet the animal withstood two to three lethal doses of the antigen. It is very difficult to say how the peptone acted. It possibly protected the antibody in the cells by producing a substance in the blood which neutralized the antigen.

Method.

It appeared to me that a combination of these methods would be more useful in asthma than one of them—that is to say, the use of the peptone and serum agar together—as they act in an entirely different manner, yet bring about in animals the same result practically. The colloidal solution is made by withdrawing two or three ounces of blood from the larger vein in the bend of the elbow into a 4-oz. tube. The arm is bandaged above and a short but wide needle introduced. The needle is attached by very short rubber tubing to a small glass tube which passes through a narrow cork fitting into the mouth of the large tube. Another small glass tube just penetrates the cork to allow the escape of air.* In about two or three minutes the tube will be half or three-quarters full. Not a drop of blood may escape. The tube is then corked with a rubber cork and left at room temperature until the next day, when the serum is pipetted off. It is best for the patient not to partake of any food for five hours previously, as the serum will then be clear. A solution of agar made by boiling 1 part in 1,000 or 1,020 of saline, is then taken, and one-fifth added to four-fifths of the serum. It is shaken up and incubated for an hour at 37° to 40° C. It will be seen how minute a quantity of agar is added, as

only one-tenth of a grain is added to an ounce of serum; 2 c.cm. will contain only 1/150 grain of agar. This is much weaker than that used by Bordet, Dale, and others, but to test its efficacy I took some of the serum agar to Dr. Anrep, then of University College, who kindly tried it in guinea-pigs. A guinea-pig weighing 380 grams received 2 c.cm. of serum agar into the femoral vein. It was ill about twenty minutes. The temperature fell from 38.3° to 36.3° C. Its hair was elevated and it shuddered markedly. It did not move. Another guinea-pig weighing 450 grams similarly received 4 c.cm. The same symptoms occurred. Its hair became erected and it rubbed its nose; it also had rigors, and coughed. In about half an hour it recovered. Dr. Anrep also tried plain serum in another guinea-pig, giving 5 c.cm., but nothing occurred. "The stuff," he writes, "is no doubt toxic, but not enough to cause a real shock."

When the serum agar has been incubated for an hour, peptone powder is mixed with it in the required percentage. I found that if 5 per cent. peptone is first added it may have the effect of inducing the asthma, though this passes off after four or five injections. This only occurs in some cases. It is better to add 2½ or 3 per cent. peptone at first. Incubate for another hour, when all the peptone will have dissolved. Then mix 0.5 per cent. phenol with about 15 minims of saline, shake up thoroughly, and pour half into the serum, shaking well, then the other half. The colloidal solution, poured into a glass-stoppered sterile bottle, is now ready for use.

Though the effect of serum agar is marked in the guinea-pig, it has no general action on human beings even when incubated with peptone. There is, however, a momentary heating of the face on injection.

In a patient in whom the asthma is quiescent the peptoned serum agar is slowly introduced into the vein twice weekly in doses of 1½ c.cm., 2 c.cm., 2 c.cm., 2½ c.cm., 3 c.cm., and 3½ c.cm. After this 2½ per cent. peptone is added again and incubated as before. Then give 2 c.cm., 2 c.cm., 2½ c.cm., 2½ c.cm., 3 c.cm., 3½ c.cm., and 4 c.cm. If the patient is better reduce to 3 c.cm., 2 c.cm., and 1½ c.cm. Of course, this may have to be altered, but it is given as a guide.

Illustrative Cases.

I will now give a few cases wherein the effect of this treatment becomes apparent.

A woman, aged 54, came on May 19th, 1925. She was recommended by Dr. Hawthorne. Had had asthma since she was 21. Her father had it. Had vaccines (autogenous) made which did her harm. She had many rhonchi on expiration. No endocrine defect apparent. No protein reactions. I gave her sixteen peptone injections intravenously, beginning with 5 minims of a 5 per cent. solution, and increased by 3 minims twice a week until she had 3 c.cm., then gradually came down to 1 c.cm. After this she was quite well and remained so for a year. The asthma returned and she only had a fortnight to spare. I gave her four peptoned serum injections of considerable size. The asthma left her and she did not return for about nine months, when she had a slight, but very slight, recurrence, which soon left her.

The asthma in the above case responded well to the peptone, but the quick result of the new injections was very striking.

A man, aged 38, had been short of wind from childhood. Since June, 1926, he had had severe attacks of asthma with a good deal of expectation. He went to Southsea, and was treated by Dr. Atholl Robertson with fifteen intramuscular peptone injections, but was no better. He had attacks night and day. He was a healthy-looking subject, with a good chest expansion. All proteins and animal substances were tried, but gave no reaction. I began with 1½ c.cm. of peptoned serum agar, and then 2 c.cm., 2½ c.cm., and 3 c.cm. He had some severe attacks of asthma during the first five injections, and was attended by Dr. Arthur Quennell of Brentwood. I then lowered his percentage of peptone, as I had begun with 5 per cent. He had no more asthma, and though for some months he had some nocturnal wheezing which was relieved by euphine, he has had no asthmatic attack and he continues well.

The next case is that of a woman who had been twenty years asthmatic, and had tried everything for it—vaccines, autogenous and stock, intramuscular peptone, etc.—and was no better.

The patient was brought to me by Dr. Wilson Smith of Harrow. She was aged 47 and had several children. She looked healthy, but thin. I began with 1½ c.cm. and went up to 4½ c.cm. She stood it very well and was looking healthier. Her blood had improved greatly. There was no facial redness. Then she had

* The original of this was shown to me by Mr. Gover of Guy's Hospital. The apparatus must be well cleaned after use.

3 c.cm. for the tenth and 2 c.cm. for the eleventh injection. She had no asthma all this time, though previously she was confined to bed every two or three weeks. She has remained well, except for two slight attacks in about three months.

In view of the fact that she had tried everything previously with no benefit, this case was very striking, and showed the rapidity with which the peptoned serum agar acted.

A man, aged 27, was sent to me by Dr. Randall of Wimbledon on November 24th, 1926. He had had asthma since he was 17. It is in his family. He went to Shanklin one year and was so bad that he had to leave. Then he went another year and was never better. This is a curious fact. I asked Dr. Randall to give him peptone, which he did intramuscularly, with but little effect. I then gave him nine injections of peptoned serum agar, from 1½ c.cm. to 4 c.cm. During the first three or four injections his asthma was but little better. It then entirely disappeared. Dr. Randall gave him the last three injections—2 c.cm., 1½ c.cm., and 1 c.cm. He remained quite well for about six weeks. Then he took a change, which made the asthma come back a little. He is now free from attacks, but is a little wheezy at night some-times. He writes that he is highly satisfied with his condition.

These are cases of great interest, and show the treatment to be very valuable. But I have had a few cases which did not respond to it; these form a very small percentage.

Women are much more subject to endocrine disturbance than men. The thyroid and the ovaries are the principal offenders.

A girl, aged 12, was brought to me from Lichfield by her mother. She looked healthy and was well grown. Her sister had horse asthma. I ordered peptone for her, which was given by her school doctor intramuscularly. She was no better. Dr. Rowlands of Lichfield then injected it into the vein, when she greatly improved, but the asthma returned. She was brought back to me in September, 1926. Her mother told me she had menstruated, but it was very scanty. I ordered her 1 grain of thyroid extract a day, and 5 grains of ovarian extract twice a day. I also prepared peptoned serum agar for her, and Dr. Rowlands gave her the injections. She has been quite well since. Her menses became much more profuse after the tablets of ovarian substance.

It will be noted that though intramuscular injections of peptone did her little good, yet she was much better after those given intravenously. I do not consider a patient should be left without trying the intravenous method. I give the intramuscular (in the back of the upper arm) only in young children and weak elderly persons. But, although quite safe, the majority of doctors do not like giving it intravenously.

The ovaries contain a hormone which has been much inquired into lately. Pratt⁸ declares that it exists in the Graafian follicles, corpus luteum, and placenta. S. Asdell and F. Marshall, F.R.S.,⁹ state that the hormone injected subcutaneously produces typical pro-oestrous change in the uterus of the bitch and changes in the vaginal epithelium.

Some (Coca, etc.) consider that asthma and hay fever are allergies, but they are not anaphylactic. I believe that, though they are allergies, they are of the family of "toxic idiopathies," and are to be considered anaphylactic. An allergy differs from an artificial anaphylaxis, as an allergic patient will react the first time he comes in contact with a protein to which he is naturally sensitive. Allergy has the same fundamental nature as anaphylaxis; I have discussed this elsewhere.¹⁰ Huber and Koessler¹¹ place the pollen extracts as antigens, producing characteristic anaphylactic reactions in guinea-pigs, and antibodies are found in the blood of properly sensitized animals, also positive broncho-constriction is produced. The view of Coca has been adversely criticized by van Leeuwen in his recent work on allergic diseases.

Peptoned serum agar must be prepared very carefully. The greatest care must also be made in injecting it into the vein, which must be done slowly. I always use a No. 12 needle. The piston of the syringe must always be withdrawn a little when the needle is supposed to be in the vein, and if some blood comes into it, it is all right. Otherwise trouble may ensue. Those who make and give it properly will be well rewarded.

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THE TREATMENT OF DIABETICS AS HOSPITAL OUT-PATIENTS.*

BY

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THE difficulties in the way of the successful investigation and treatment of diabetes mellitus in the ordinary out-patient department of a general hospital are familiar to every physician. At the Salford Royal Hospital an attempt has been made to meet them in a special out-patients' clinic for all diabetic cases. The clinic has been in my charge under the direction of the honorary medical staff.

In presenting this account of the first year's working of the clinic it must be pointed out that the work has not been undertaken from the "research" point of view, but as a matter of necessity, and that nearly all our patients are of the labouring class, uneducated and financially badly off—not at all promising material for elaborate dietetic treatment. A few were of the artisan class, one a clerk, and one—an incorrigible carbohydrate "smuggler"—was a schoolmistress.

The functions of the clinic are investigation and control of patients who are sent to the clinic from the wards, from the general out-patient department, and occasionally direct from the practitioner.

All cases were divided, before investigation, into the two groups of severe diabetes mellitus, and of glycosuria of other origin. In the first group were included all cases with ketosis or a short acute history, and all cases in young adults and children. Such patients were immediately admitted to the wards for full investigation and control before re-discharge to the clinic. The second group consisted of patients whom it was thought safe to investigate as out-patients. Investigation consisted of blood and urinary analysis and of sugar tolerance curves; the latter, unfortunately, were not always possible to perform owing to pressure of work, but they were performed in at least all doubtful cases. In a few instances patients were admitted to the wards for a day or two for tolerance estimation.

Classification of Cases.

After investigation all cases were classified into four groups. Group I consisted of all cases considered on clinical grounds to be definite diabetes mellitus. Group II consisted of diabetics of the milder elderly type, whose blood sugar—taken four hours after breakfast—was constantly at or about 0.180 per cent. or more; whose urine contained sugar, often in large amount, but no acetone; and whose weight remained constant or even increased. This group corresponds roughly to the hepatic group of Maclean,¹ and it is supposed that these are primarily cases of defective storage by the liver. The patients in this group were nearly all of obese type, and, with one exception, were over 45 years of age. It is certain that such persons tend to develop a condition of true diabetes mellitus, though of a mild type. Group III consisted of patients—clinically midway between the other two groups—supposedly in this category. Group IV contained three cases.

One woman of 70 had a glucose tolerance normal for her age and some glycosuria. She was considered to be a case of the "normal glycosuria of the elderly" described by Langley.² The other two cases in the group were glycosuria of renal origin. Their progress was interesting. The first cleared up entirely in a few weeks. The second, after remaining at a normal blood sugar level for three months, presented herself at the clinic one day with acetoneuria and a blood sugar of 0.285 per cent. This patient has not attended the clinic since, but it is known that she is being treated with insulin by her own doctor.

TABLE I.—Classification of Cases.

Group.	No. of Cases.
I. Diabetes mellitus	20
II. Elderly hepatic type	14
III. Elderly mellitus type	10
IV. Non-diabetic glycosuria	3
Total	47

There were five additional cases, but they are not included in the table as their investigation was not completed.

* A paper read before the Salford Division of the British Medical Association.